CHEMICALS MEETING THE CRITIERIA FOR LISTING AS DEVELOPMENTAL AND REPRODUCTIVE TOXICANTS (DARTs) VIA THE AUTHORITATIVE BODIES MECHANISM: DIURON, IDENTIFIED BY U.S. EPA

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Diuron meets the criteria for listing under Proposition 65 via the authoritative bodies listing mechanism. The regulatory guidance for listing by this mechanism is set forth in Title 22, California Code of Regulations (CCR), Section 12306. For example, the regulations include provisions covering the criteria for evaluating the documentation and scientific findings by the authoritative body to determine whether listing under Proposition 65 is required.

The U.S. Environmental Protection Agency (U.S. EPA) has been identified as an authoritative body for purposes of Proposition 65 (22 CCR Section 12306(l)) and has identified diuron as causing developmental or reproductive toxicity. This was done by that Agency in implementing its Toxic Release Inventory (TRI) program (*i.e.*, Section 313 of the Emergency Planning and Community Right-to-Know Act of 1986 (EPCRA)). On the basis of identifying chemicals which caused reproductive, developmental and/or other toxicities the U.S. EPA added a number of chemicals to the TRI list. The U.S. EPA published its toxicity findings in the *Federal Register* (**59:**1788-1859, 1994 and **59:**61432-61485, 1994). In proposing specific chemicals for addition to the TRI list, the Agency stated that a hazard assessment was performed for each candidate, "…in accordance with relevant EPA guidelines for each adverse human health or environmental effect…" (*Federal Register* **59:**1790).

OEHHA has found that diuron has been "formally identified" as causing reproductive toxicity according to the regulations covering this issue (22 CCR 12306(d)) because the chemical has "been identified as causing … reproductive toxicity by the authoritative body" (*i.e.*, U.S. EPA) "in a document that indicates that such identification is a final action" (*i.e.*, the TRI *Final Rule* (*Federal Register* **59:**61432)) and has "been included on a list of chemicals causing … reproductive toxicity issued by the authoritative body" "and the document specifically and accurately identifies the chemical" and has been "published by the authoritative body in a publication, such as, but not limited to the federal register…"

OEHHA also finds that the criteria for "as causing reproductive toxicity" given in regulation (22 CCR 12306(g)) have been satisfied for diuron (CAS No. 148-79-9). In making this evaluation, OEHHA relied upon the documents and reports cited by

U.S. EPA in making their finding that this chemical causes reproductive toxicity (for the developmental endpoint). OEHHA consulted additional sources of information on the specific studies cited by U.S. EPA. This was done only where necessary to affirm or clarify details of results and study design for studies cited by U.S. EPA.

A major source of information used by the U.S. EPA in its TRI evaluations was the "Tox-Oneliner" database maintained by U.S. EPA's Office of Pesticide Programs (OPP). This database consists of brief summaries of (usually unpublished) data submitted to the Agency in compliance with regulatory requirements. Many database entries include a notation of "core grade" – a system formerly used by U.S. EPA to indicate the extent to which a study conformed to published test guidelines (U.S. EPA 1983a and 1983b). Under this scheme, a "core grade guideline" study was considered to meet all guideline requirements; a "core grade minimum" study was considered sufficient for risk assessment; and a "core grade supplementary study" was considered to provide useful supplementary information, but not to be suitable for risk assessment on its own.

Studies cited by U.S. EPA in making findings with regard to reproductive toxicity are discussed below. The statements in bold reflect data and conclusions which appear to satisfy the criteria for sufficiency of evidence for reproductive toxicity in regulation (22 CCR 12306[g]). Where a notation of "not stated" has been made, OEHHA staff were unable to find an explicit statement of a particular detail such as the number of animals in each dose group. Where NOELs (no-observed-effect-level), LOELs (lowest-observed-effect-level), or LELs (lowest-effect-level) are included in the study descriptions below, they are quoted directly from the cited references.

Diuron (CAS No. 330-54-1)

Developmental toxicity **has been manifested as skeletal anomalies and decreased body weights.**

The US Environmental Protection Agency (US EPA, 1994a and 1994b) concluded that "…there is sufficient evidence for listing diuron on EPCRA section 313 pursuant to EPCRA section 313(d)(2)(B) based on the…developmental toxicity data for this chemical."

Supporting documentation for the TRI listing (US EPA, 1993a) states, "Offspring of Wistar rats fed diuron during gestation days 6-15 demonstrated an increase in fetotoxic effects including wavy ribs, extra ribs, and delayed ossification. The developmental LOAEL in this study was 100 mg/kg/day; no NOEL was determined. Maternal and fetal body weights decreased at 400 mg/kg/day (IRIS; US EPA, 1993b). In a three-generation reproduction study in rats fed 6.25 mg/kg/day, decreased body weights were reported in the F_{2b} and F_{3a} litters (IRIS; US EPA 1993b); however, only one dose was tested."

The two primary studies on which the TRI listing is based for diuron, the rat teratology and the rat three-generation reproduction study, have been described in the published literature (Khera et al., 1979; Hodge et al., 1967).

In the rat teratology study (Khera et al., 1979), there were significant decreases in maternal and fetal weights at the high dose of 500 mg diuron/kg bw/day, given by gavage on gestation days 6 - 15. The frequency of wavy ribs was increased over controls in all three diuron-treated groups; the increases were statistically significant at the mid and high dose. Delayed ossification of the calvarium was observed in all groups, with a statistically significant increase over controls at the low dose of 125 mg diuron/kg bw/day. US EPA (1988), determined a LOAEL of 125 mg diuron/kg bw/day, based upon the ossification effects observed at that dose. As this was the lowest dose tested, no NOAEL was established.

For the three-generation rat reproduction study (Hodge et al., 1967), animals were given food which contained diuron at concentrations of either 0 or 125 ppm. Neither the fertility index nor the average number of pups per litter was altered by exposure to diuron. There was some evidence for adverse effects on postnatal growth of the F_{2b} and F_{3a} generations, but this finding was not repeated when the study was replicated.

An additional rat developmental toxicity study (Dearlove et al., 1986) and an additional rat reproduction study (Cook, 1990) were submitted to OEHHA. The developmental study (Dearlove et al., 1986) reported decreased fetal body weight and delayed ossification after administration of 400 mg/kg diuron on days 6-15 of gestation. Maternal toxicity at this dose was manifested as reduced body weight and weight gain, and reduced food intake. In the reproduction study by Cook (1990), significantly decreased birthweight in the F_1 generation and decreased pup weights at postnatal days 4, 7, 14 and 21 were reported at a dose level of 1750 ppm in diet. In the F_2 generation, significant decrements in pup weight were reported at postnatal days 7, 14 and 21 at the same dose level.

With regard to the studies cited as supporting US EPA's action in adding a chemical to the EPCRA-TRI list, OEHHA finds that the evidence for DART effects appears to meet the criteria of 22 CCR12306, and notes the following:

1. **Adequacy of the experimental design:**
   Study a) rat teratology study - IRIS (US EPA, 1993b) states that this study is core grade supplementary. This grade was probably given due to the numbers of animals per dose group, which is slightly lower than that specified by US EPA testing guidelines (US EPA, 1983a). However, the use of this study as the basis for the 10-day Health Advisory for Diuron in drinking water (US EPA, 1988), indicates that the Agency determined the data were suitable for risk assessment.
   Study b) rat 3-generation reproduction study - IRIS (US EPA, 1993b) states that no core grade was given for this study.
2. **Route of Administration:**
   Study a) rat teratology study - oral gavage.
   Study b) rat 3-generation reproduction study - oral, in diet.

3. **The frequency and duration of exposure:**
   Study a) rat teratology study - each of gestation days 6-15.
   Study b) rat 3-generation reproduction study - continuous, in diet.
4. **The numbers of test animals:**
   Study a) rat teratology study - 14-19 pregnant dams per dose group.
   Study b) rat 3-generation reproduction study - 8 males and 16 females per group, study repeated once with the same numbers of animals.
5. **The choice of species:**
   The rat is a standard test species.
6. **The choice of dosage levels:**
   Study a) rat teratology study - 0, 125, 250, 500 mg/kg/day; when corrected for 80% active ingredient, the dose levels were 0, 100, 200, 400 mg/kg/day (US EPA, 1993b).
   Study b) rat 3-generation reproduction study - 0 and 125 ppm (0 and 6.25 mg/kg/day, US EPA, 1993b).
7. **Maternal toxicity:**
   Study a) rat teratology study - maternal body weight was decreased at the highest dose tested (500 mg/kg/day).
   Study b) rat 3-generation reproduction study - no maternal toxicity reported.

References

Cook JC (1990). Reproductive and Fertility Effects with Diuron (IN 14740) Multigeneration Reproduction Study in Rats. Haskel Laboratory Report No. 560-90.

Dearlove GE, Hoberman AM, and Christian MS (1986). Developmental Toxicity Study of H-16035 Administered by Gavage to Rats. Argus Research Laboratories. Protocol 104-102

Hodge HC, Downs WL, Panner BS, Smith DW, and Maynard EA (1967). Oral toxicity and metabolism of diuron (N-(3,4)-dichlorophenyl)-N',N'-dimethylurea) in rats and dogs. *Food Cosmet. Toxicol.* 5:513-531.

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